Source-to-Outcome Modeling

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Information in this presentation addresses:

- Chapters in the report
  5. Dietary exposure modeling
  6. Linking exposure models
  7. Longitudinal exposures
  8. Using model-to-measurement comparisons to evaluate model predictions
- Charge questions
  2. Longitudinal dietary exposure assessment
  4. Comparison of model predictions with human monitoring data

Modeling Oral Doses from Dietary Exposures

Exposure modeling

- Single day dietary exposure modeling has been performed since the late 1980s using the same basic approach
- Multiple models have been developed and evaluated by the SAP
- Conclusion from multiple model reviews
  - While models differ in certain details their results are similar for single day exposures
- Longitudinal (multiple consecutive days for one individual) is a greater challenge
  - Limited empirical data on longitudinal exposures
  - Multiple methods proposed to simulate longitudinal exposures

Exposure modeling in this project

- The PBPK/PD model is not directly linked to the exposure model - exposure data from any dietary model can be used
- Models used in this project:
  - CARES 3.0 and LifeLine 4.1
  - DEEM^{TM} 2.16 used in model comparison
- Residue data
  - Reflect recent dietary intakes (2006-2008)
  - Developed following existing EPA regulatory policies and public examples
  - Details given in Attachment C “2010 Update of the Acute Dietary Risk Assessment for Chlorpyrifos”

Results

- Models give similar estimates of daily doses
  - Within a factor of 2-3 at the 99.9th percentiles
- Doses
  - Highest in 3 year olds
  - 10 - 20% lower in infants
  - 50% lower in adults
- Consistent with age-related differences in exposures to residues of other pesticides

Linking Dietary Exposure and PBPK/PD Models

Defining the individual

- The exposure modeling precedes the PBPK/PD modeling
- The PBPK model assumptions on physiology and metabolism need to be consistent with dose estimates and an oral pathway of exposure
- Exposure models define age, gender, and bodyweight
- Output of model is therefore:
  - Age, gender, and bodyweight
  - Longitudinal dose history

Moving data between the models

- Data from dietary model is converted to an Excel file;

Age (y)	Sex 0=M, 1=F	Weight (kg)	Dose Day 1 (mg/kg)	Dose Day 2 (mg/kg)	Dose Day 3 (mg/kg)	Dose Day 4 (mg/kg)	Dose Day 5 (mg/kg)
0.5	1	6.8	3.97E-06	4.39E-07	1.12E-05	1.04E-05	1.65E-06
0.5	1	6.4	3.31E-06	9.61E-07	1.12E-05	6.78E-05	1.65E-06

- The PBPK/PD model reads this file as an input

Models view doses differently

- Exposure models define dose as:
  - Mass of residue in daily diet on a bodyweight basis (mg/kg/d)
  - Timing of dose within a 24 hour period typically not considered
- PBPK/PD model defines dose as:
  - Mass entering into the intestine compartment
  - Rate is not constant over time
- Mass entering intestine is driven by:
  - Timing of meals and fraction of dose in each meal
  - Rate of stomach emptying

Converting dietary doses to intestine loading rates

- Dietary doses:
  - Occur during multiple eating events in a day; but
  - Top 2% of population receive 75% of daily dose from one food
  - Assumed total daily dose occurs at a single meal
  - Assumption is conservative (increases estimate of peak levels in blood)
- Stomach emptying rates:
  - Time to empty first half of a meal reported as 30-90 minutes
  - A value of 90 minutes is used in the model
  - Model not sensitive for rate of transfer into the intestine

Modeling Longitudinal Exposures

Challenge of modeling longitudinal exposures

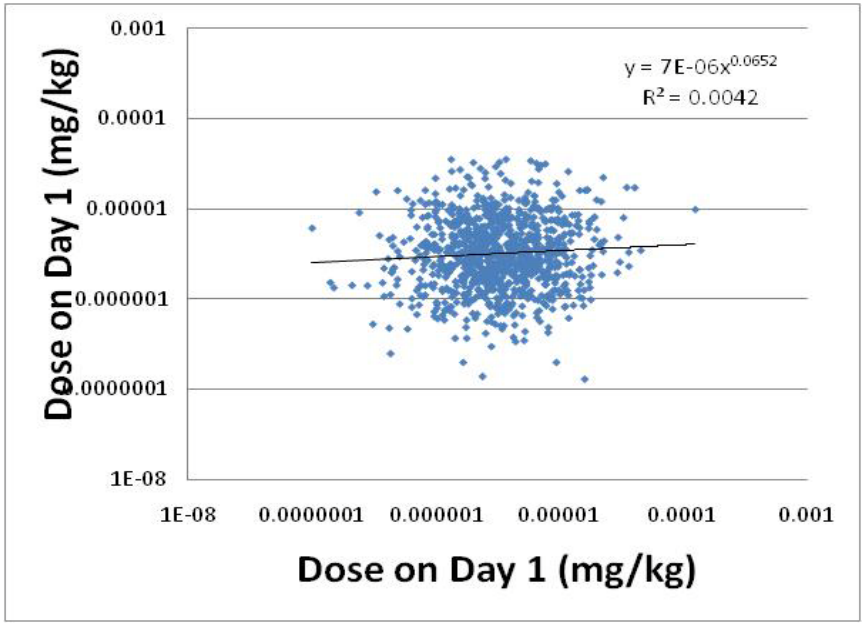
- Current dietary surveys do not collect data on an individual's dietary intakes on consecutive days
- This requires exposure modelers to simulate longitudinal dietary exposures
  - Multiple approaches have been proposed
- This introduces uncertainty in risk predictions for exposures longer than one day

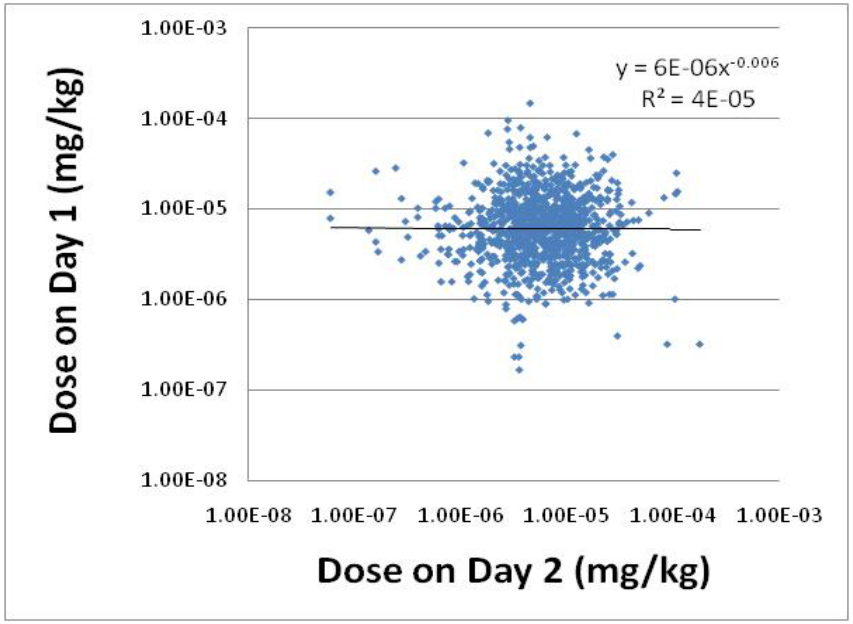
Approach used

1. Continuous exposures to constant doses
2. Different approaches for simulating longitudinal exposures
   - LifeLine seasonal, LifeLine daily, and CARES
3. Investigate impact of longitudinal exposures on adults with doses at or above 99.9th percentile dose

LifeLine random day and CARES

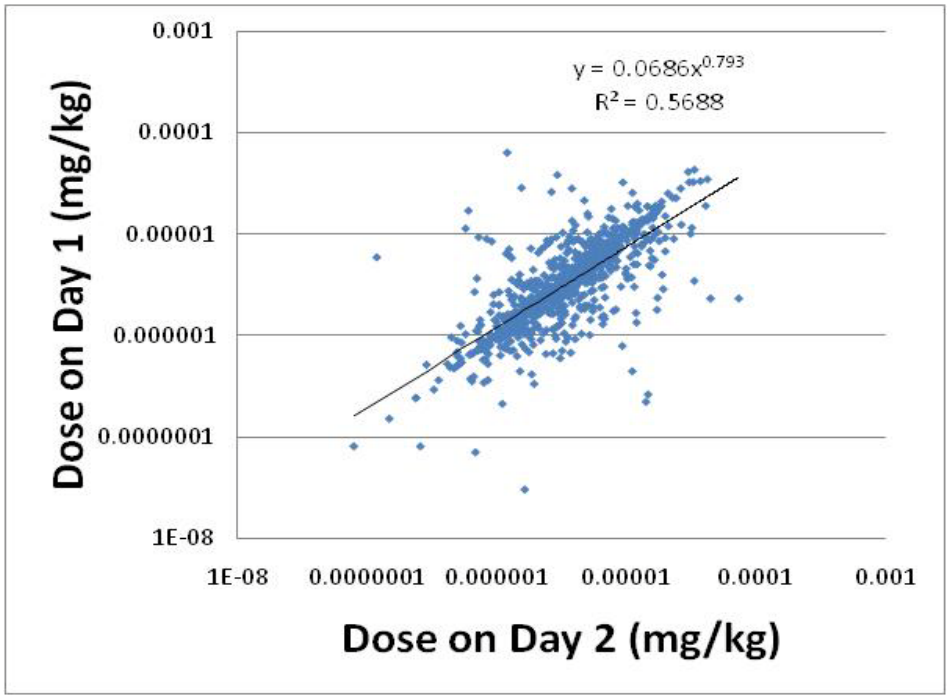
No correlation between doses on consecutive days.





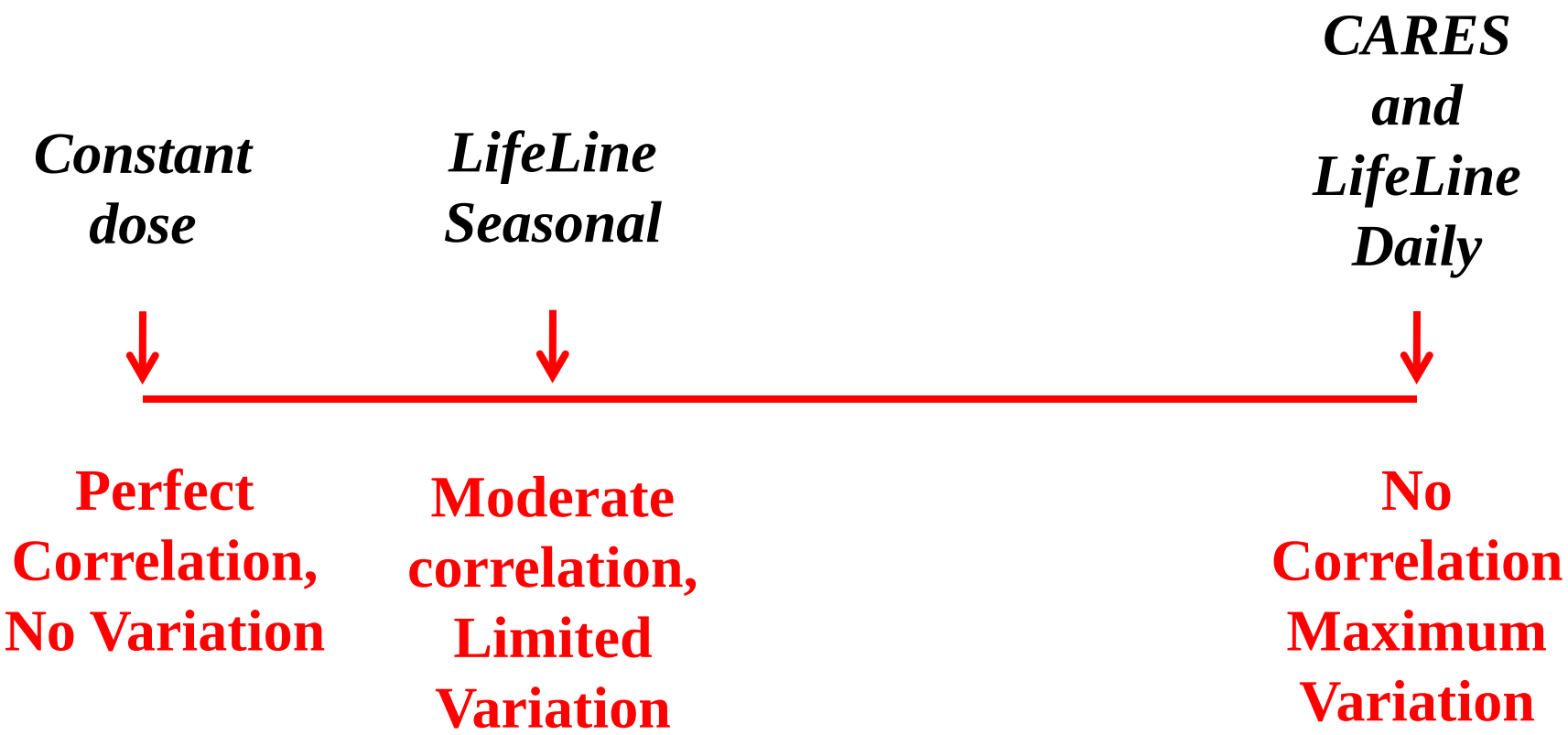
The LifeLine seasonal

Moderate correlation



Investigating impacts of longitudinal exposures: bounding the issue

All sets of data can be placed on a common scale

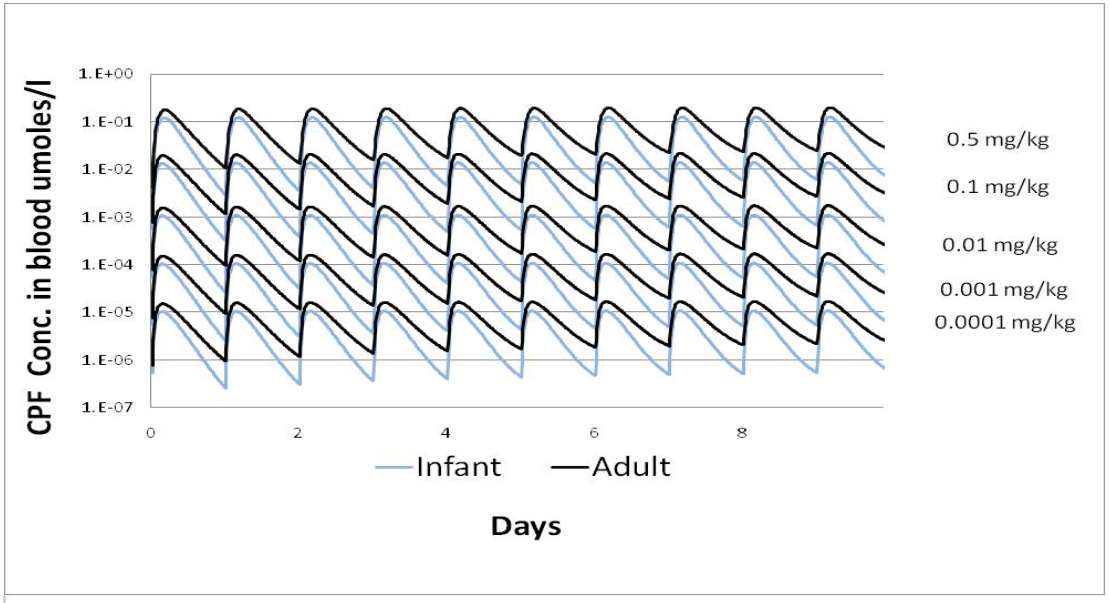


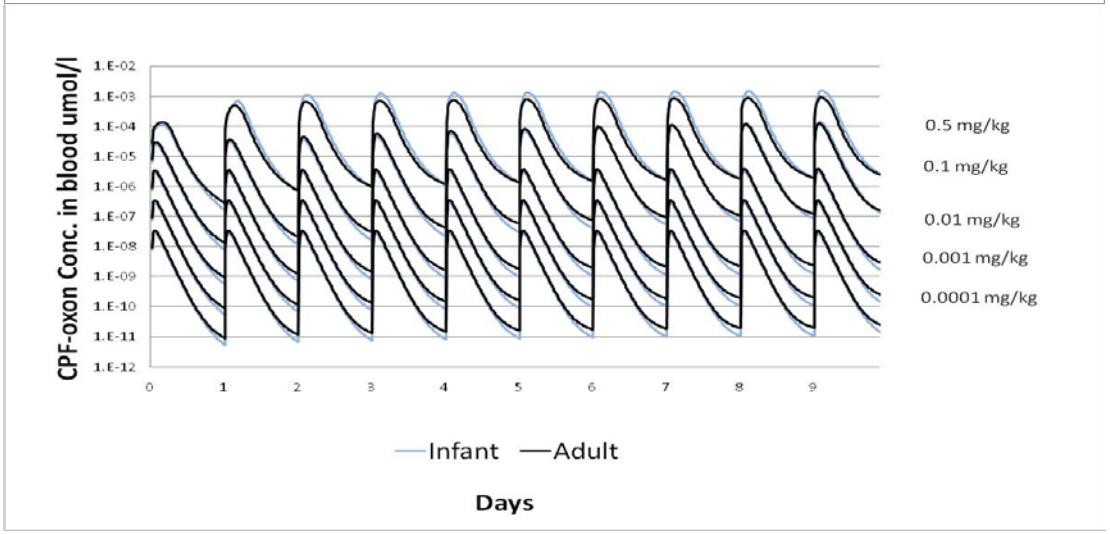
Impact of a constant dose

- Continuous exposures to constant dose were modeled for typical adult and infant over 30 days
- Five doses (0.5- 0.0001 mg/kg)
  - Doses that cause significant AChE inhibition (0.5 mg/kg)
  - Doses that occur on one day to the top 1% of 3 year olds (0.0001 mg/kg)
- Determined
  - Build up of CPF and CPF-oxon
  - Increasing inhibition of AChE

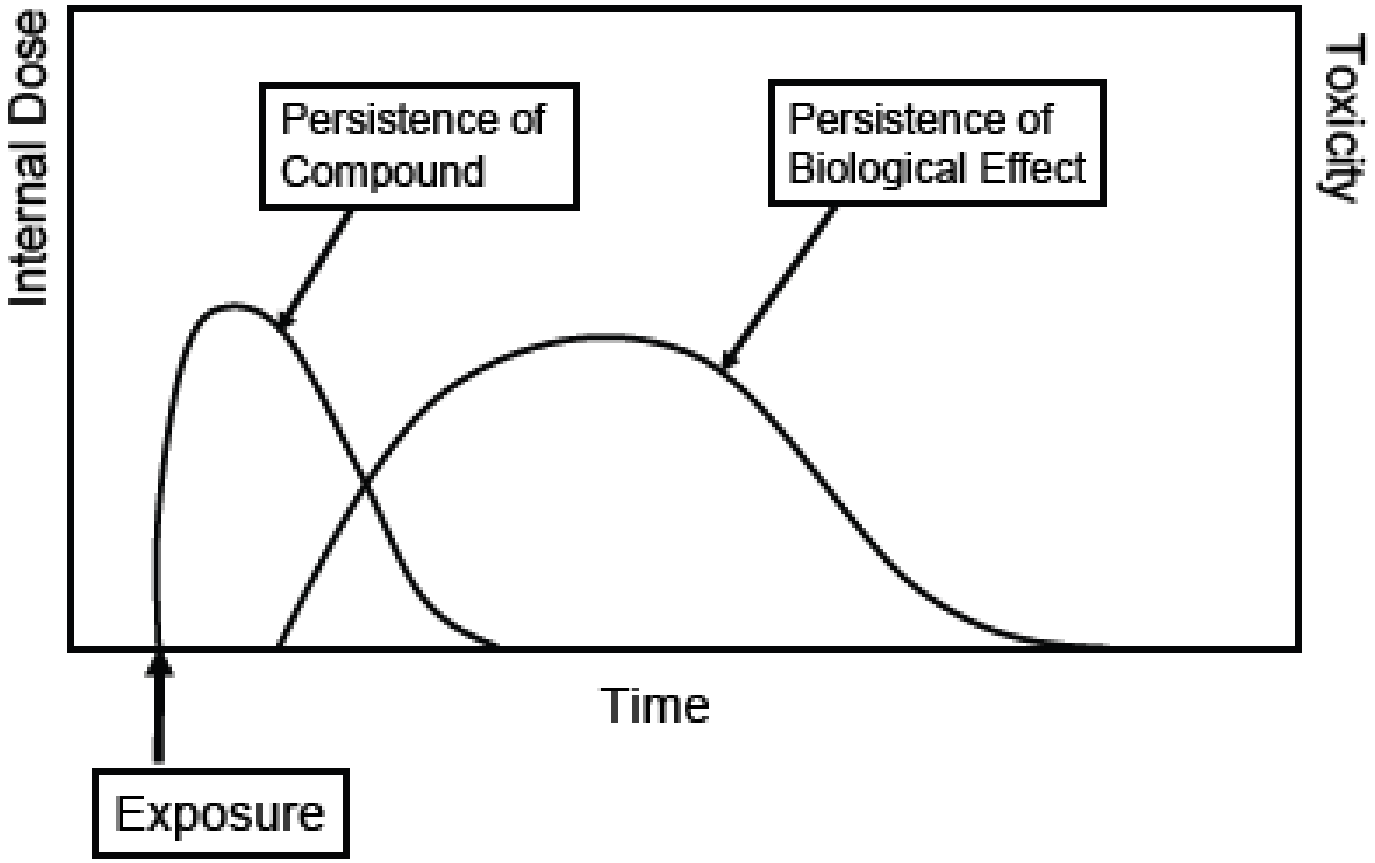
CPF and CPF-oxon levels in blood

- Levels of CPF increase slightly
  - Approximately 16% increase in peak level on day 30 vs. day 1
  - Increase not dose dependent
- Levels of CPF-oxon increase in a dose dependent manor:
  - 18 fold increase at 0.5 mg/kg
  - 1% increase at 0.0001 mg/kg



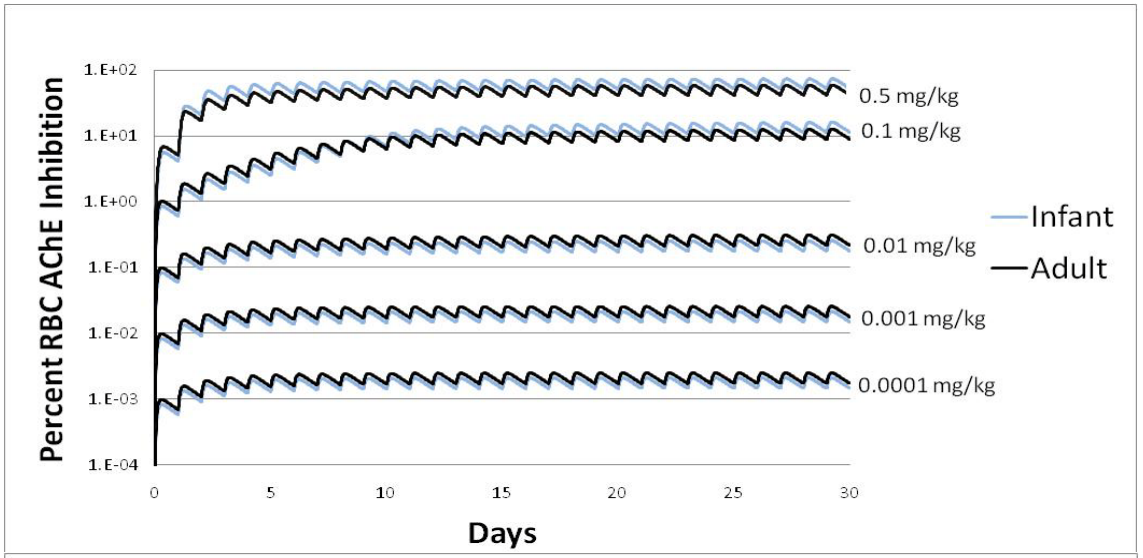


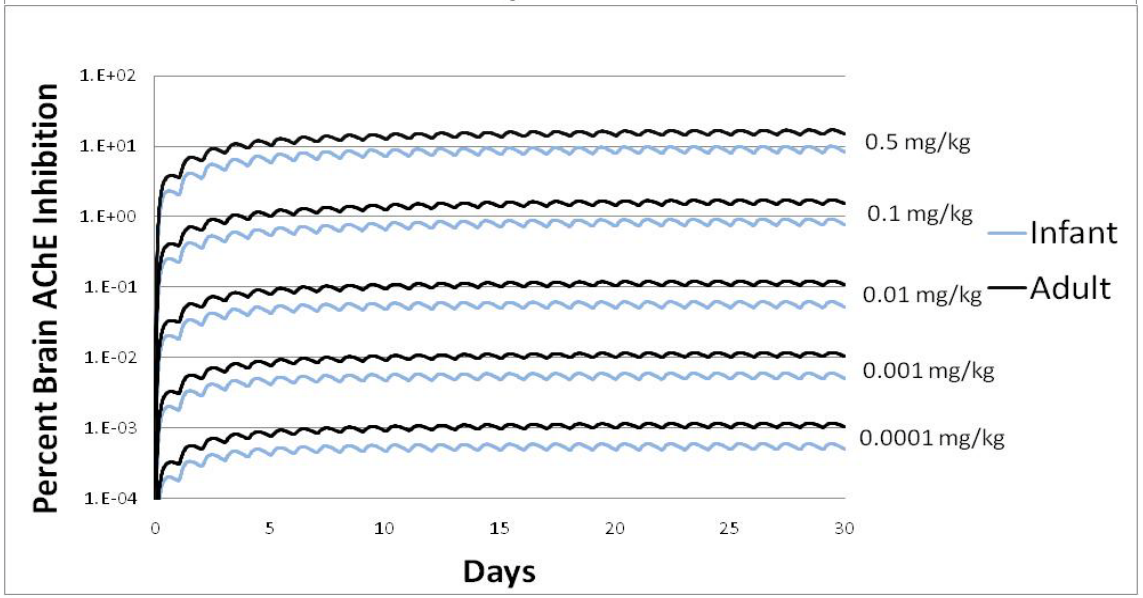
Persistence



RBC and Brain AChE Inhibition

- RBC AChE inhibition increases in a dose and age dependent manner:
  - 0.1 mg/kg adults had a 20 fold increase and infants a 12 fold increase
  - At 0.0001 mg/kg there was a 2.5 fold increase for both ages
- Brain AChE inhibition increases similar for adults and infants
  - Increases ranged from 4 fold at high dose to 3 fold at low dose



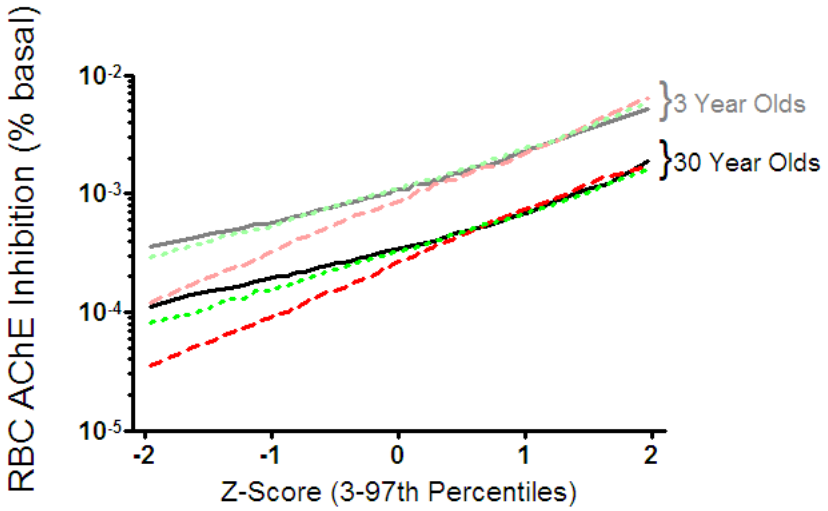


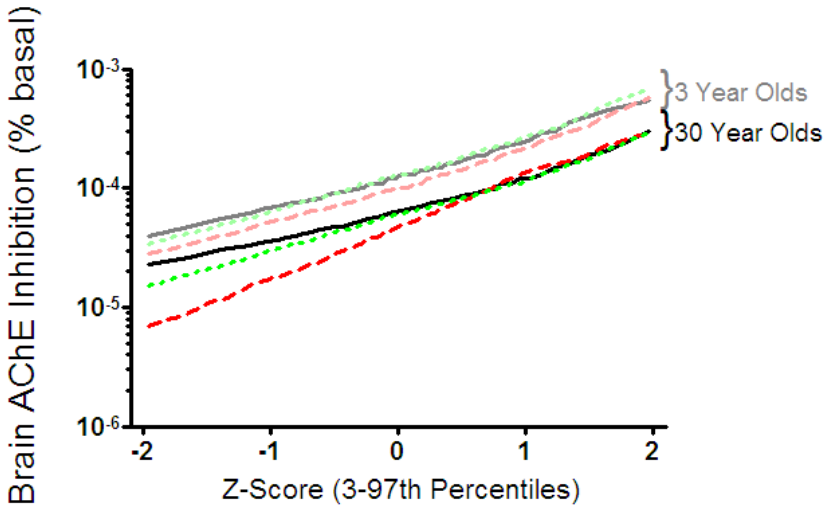
Predictions of the three longitudinal approaches for CPF and CPF-oxon

- All three approaches give similar results
- Consistent with the finding that CPF and CPF-oxon formed on one day do not carry over to the following days
  - If there is no “carry over” then differences in assumptions about exposures on prior days should have no impact

Predictions of the three approaches for AChE inhibition

Approaches differ at low exposures but agree for high exposures (top one third)





CARES LifeLine Daily LifeLine Seasonal

Why are responses in high-dose individuals independent of modeling assumptions?

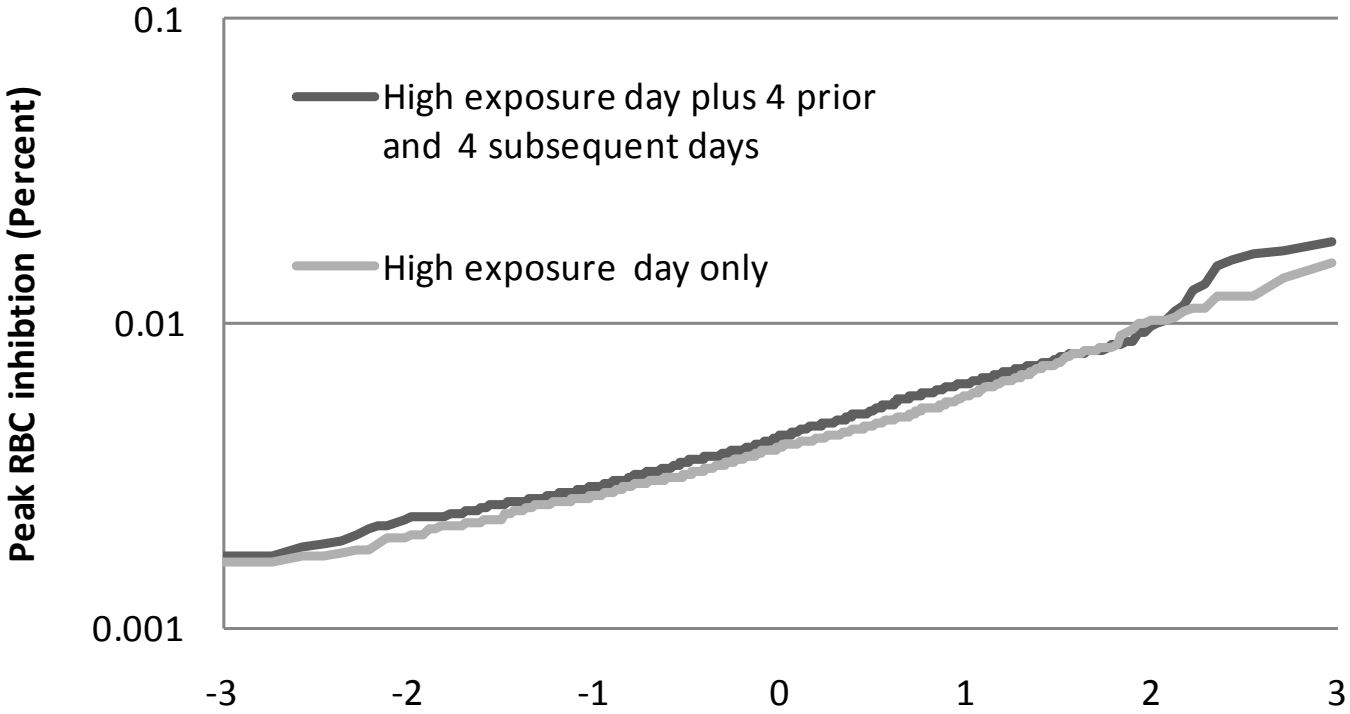
- Asymmetrical effects of high and low doses on subsequent days
  - A high dose (1000) will affect the next day even if only 10% carries over if the next day's dose is small (10)
  - 1000 *0.1 +10= 110 versus 10 (***a 11 fold change)***
  - In contrast, if the days are reversed
  - 10*0.1 + 1000 = 1001 versus 1000 (***a 0.1% change)***
- Therefore individuals receiving smaller dose are more sensitive to doses on prior days than individuals receiving high doses
  - More affected by differences in the longitudinal models

Impact of longitudinal exposures on AChE inhibition in highly-exposed individuals

- Procedure:
  - Dietary dose histories (365 days) were created for a large number of adults using CARES
  - Individuals were identified who had a “high” daily exposure (in the top 0.1% of the daily exposures received by adults) on one of the 365 days
  - The doses on the four days prior, and subsequent, to the high exposure day were identified
    - » Resulting in nine days of exposure with the high daily exposure occurring on day five
- The Variation model was used to determine impact of dietary exposures on peak RBC and brain AChE inhibition for:
  - The peak day alone; and
  - The nine days of exposures

Impact of longitudinal exposures on high exposure days

Prior an subsequent exposures increased RBC AChE inhibition by an average of 10%



EPA Scientific Advisory Panel, Washington, DC, February 15-18, 2011

Findings on Longitudinal Exposures

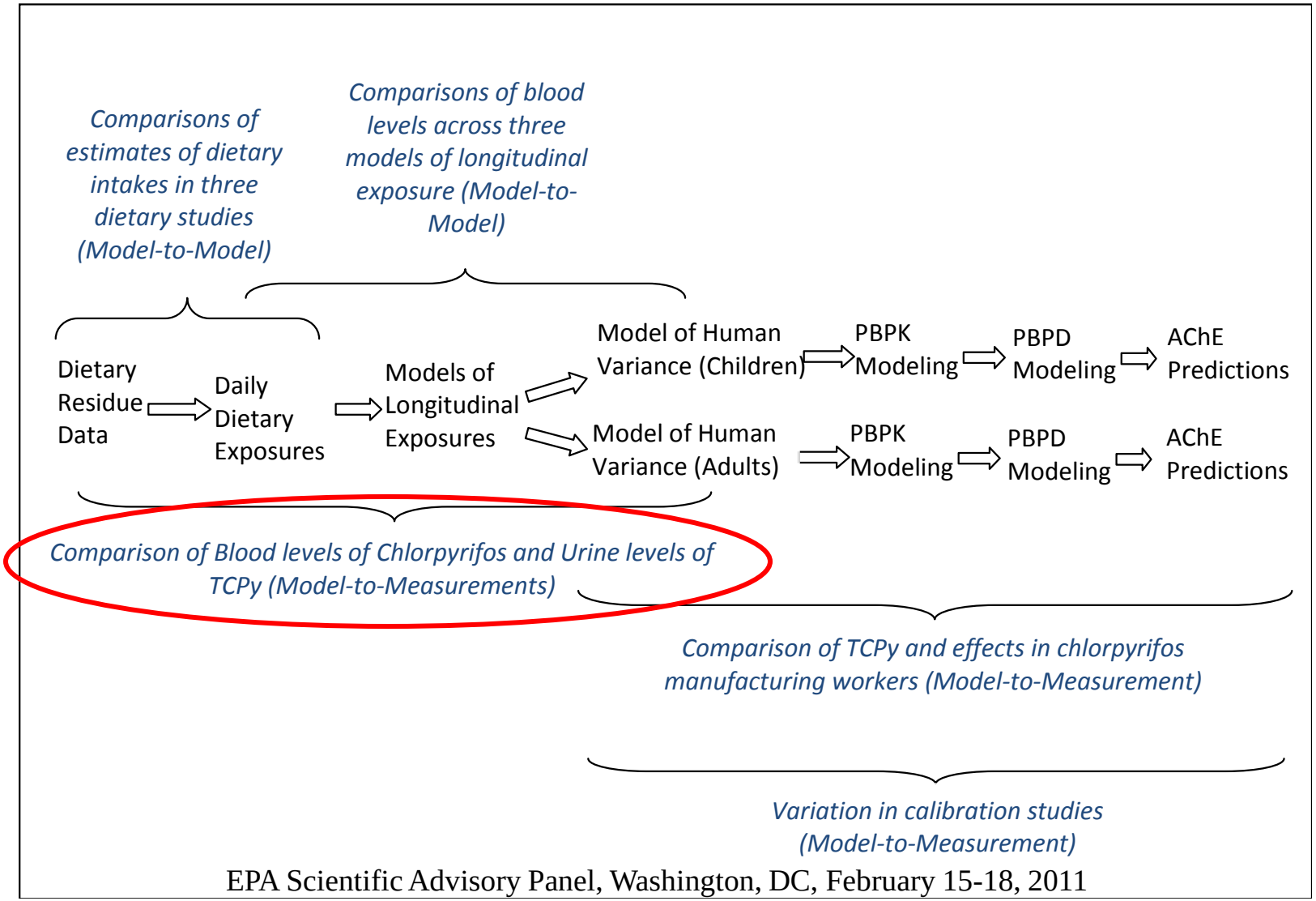
- The findings of the various analyses lead to the same conclusions on the impacts of longitudinal dietary exposures
  - CPF and CPF-oxon do not accumulate over time at dietary doses
  - AChE inhibition does increase but the impact is minimal (10%) at the 99.9th percentile
- AChE effects from dietary exposures
  - Highly exposed individuals can be predicted based on single daily doses
  - Typical- and low-exposed individuals require consideration of longitudinal exposures

Evaluating the Source-to-Outcome Model by Using Human Monitoring Data

Model-to-Measurement

- Source-to-outcome models and measured data
  - Recognizing the challenges of model evaluation
- Key strategy in model-to-measurement comparisons
- Comparisons to blood levels of CPF
- Comparisons to urinary measurements of TCPy

No one set of monitoring data can evaluate the entire source-to-outcome model



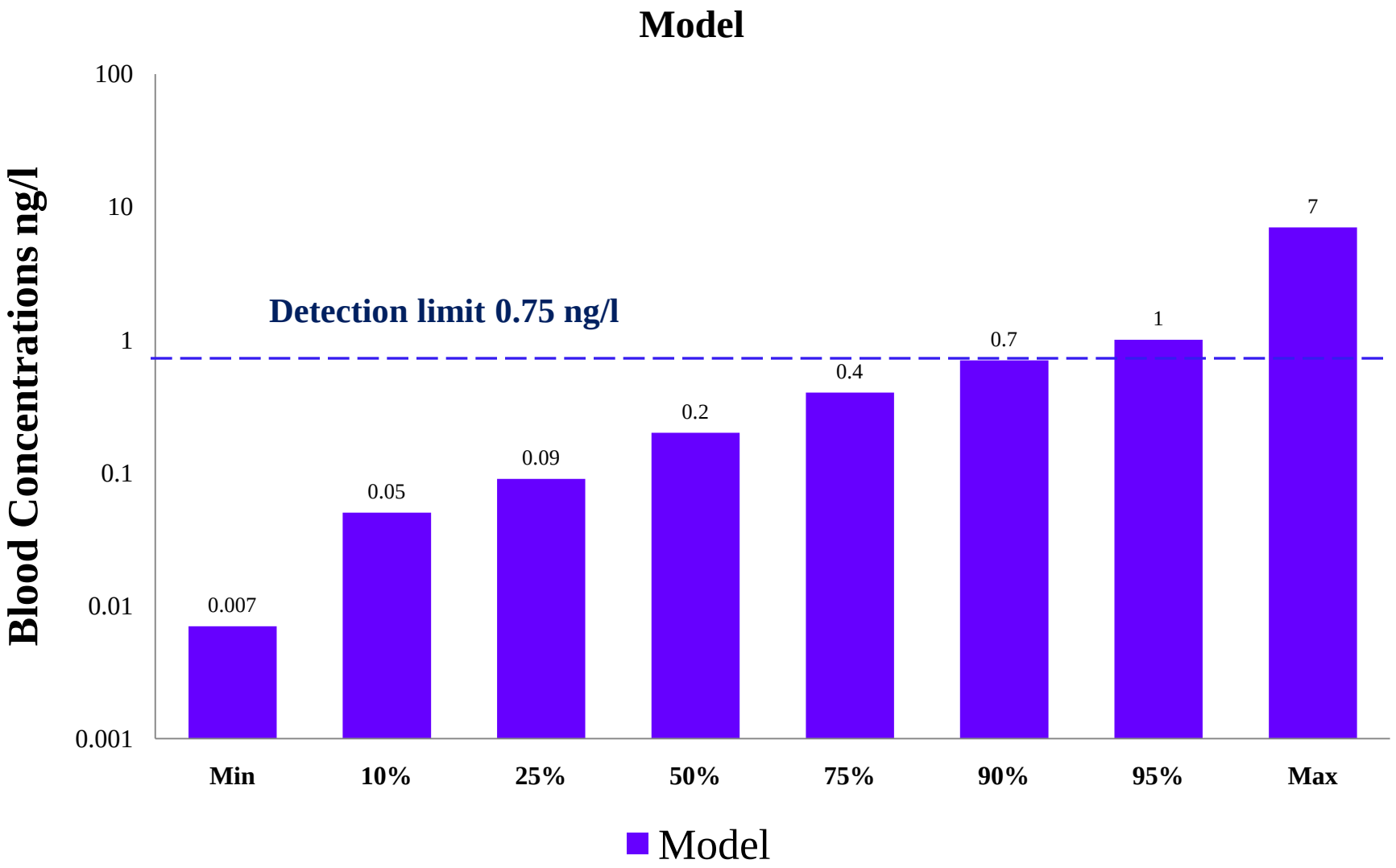
Strategy

- Measured data is produced by surveys with “characteristics” that affect their findings
  - Ages surveyed
  - Time since last exposure
  - Pregnancy
- To facilitate model-to-measurement the source-to-outcome model needs to predict results as the survey would measure them
  - Mimic survey characteristics

Comparison to survey data on blood levels of CPF

- Current levels are available from two surveys Whyatt et al. and Barr et al.
  - Data collected from mothers at the time of delivery
  - Exposures believed to be limited to dietary exposures
  - The time since last meal is not reported
- Compare to model results
  - Variation across adults
  - Levels in blood of adults at any time between 0 and 24 hours following a dietary exposure
  - Adjusted to reflect pregnancy

Model-to-Measurement Results



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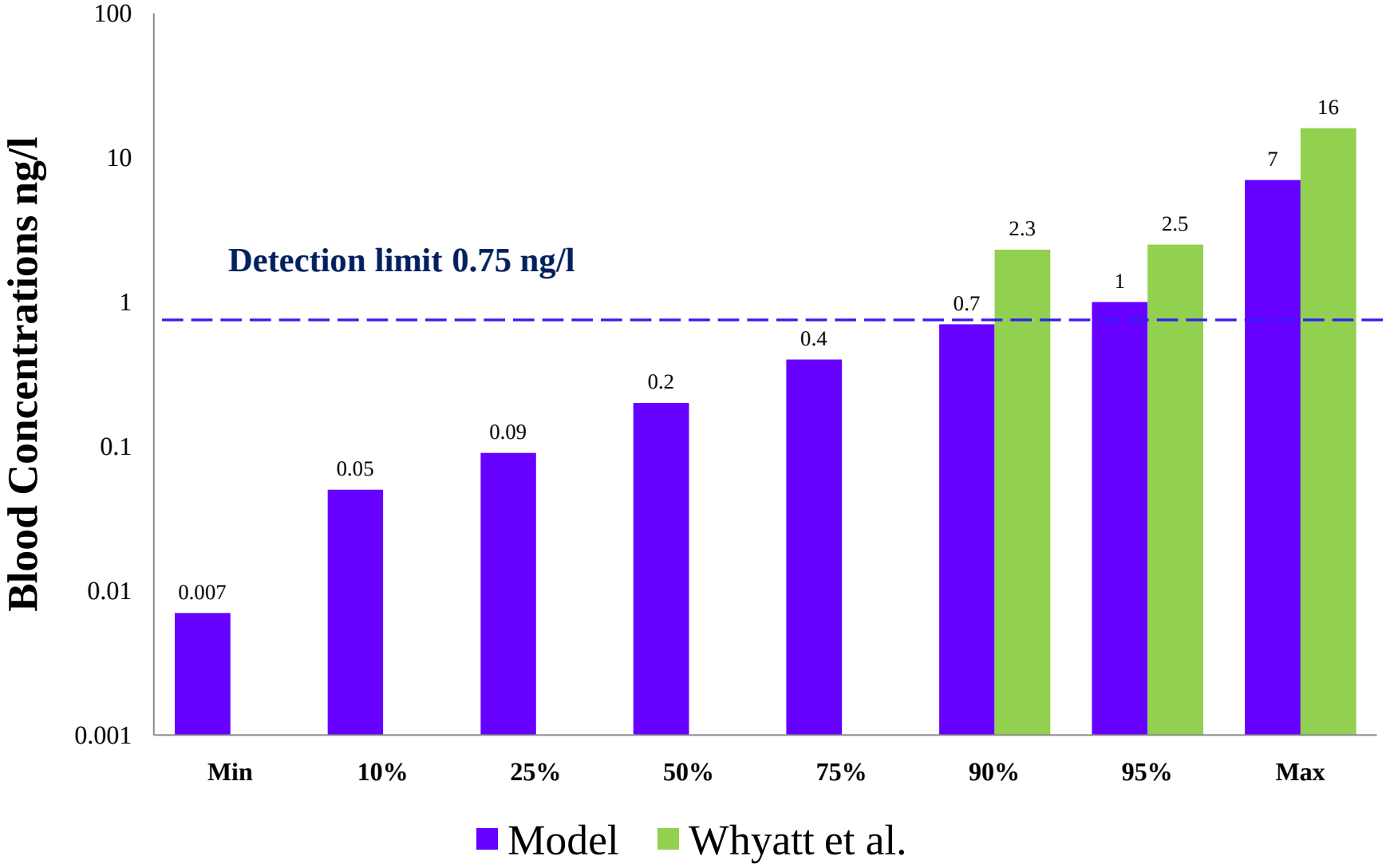

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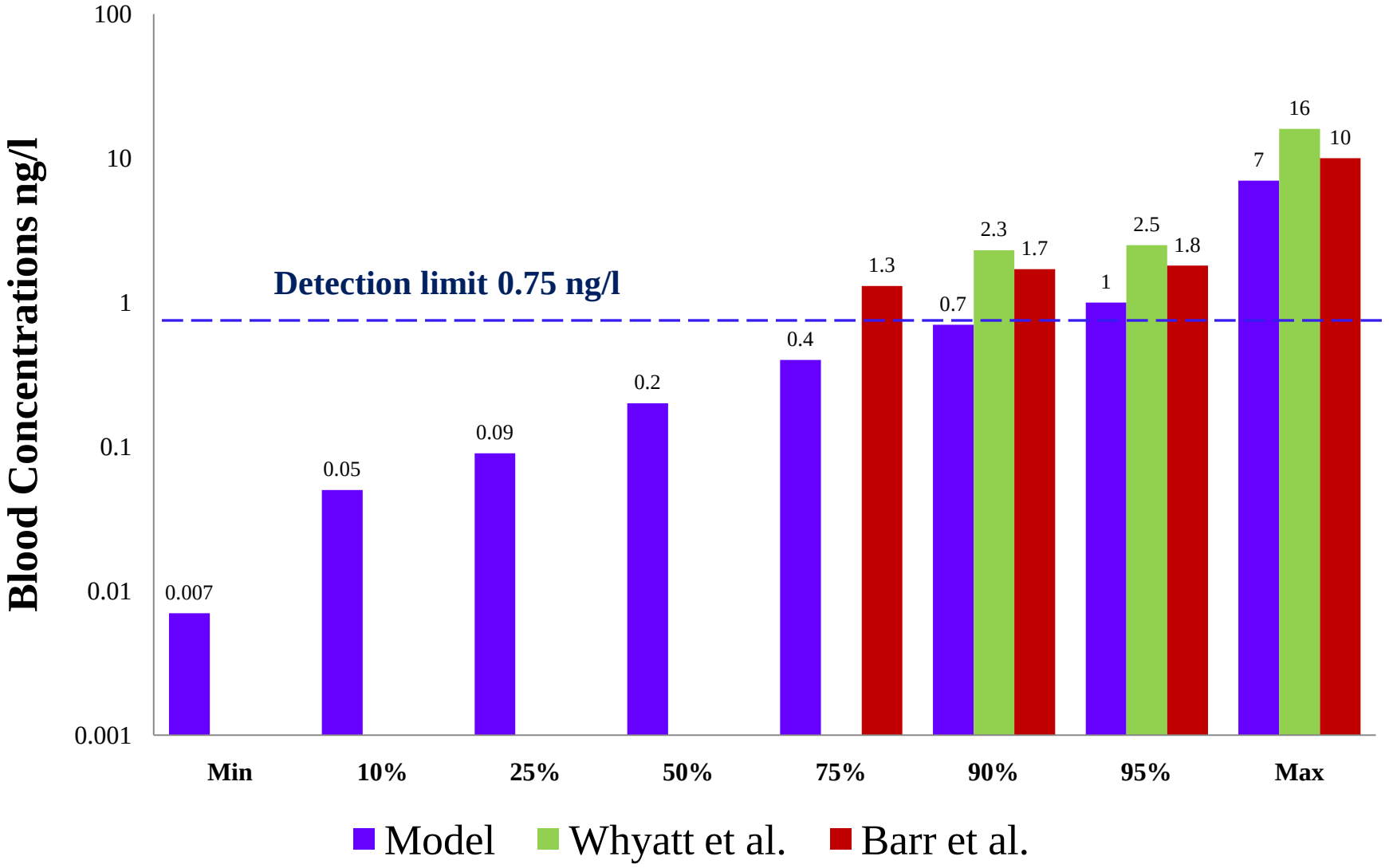
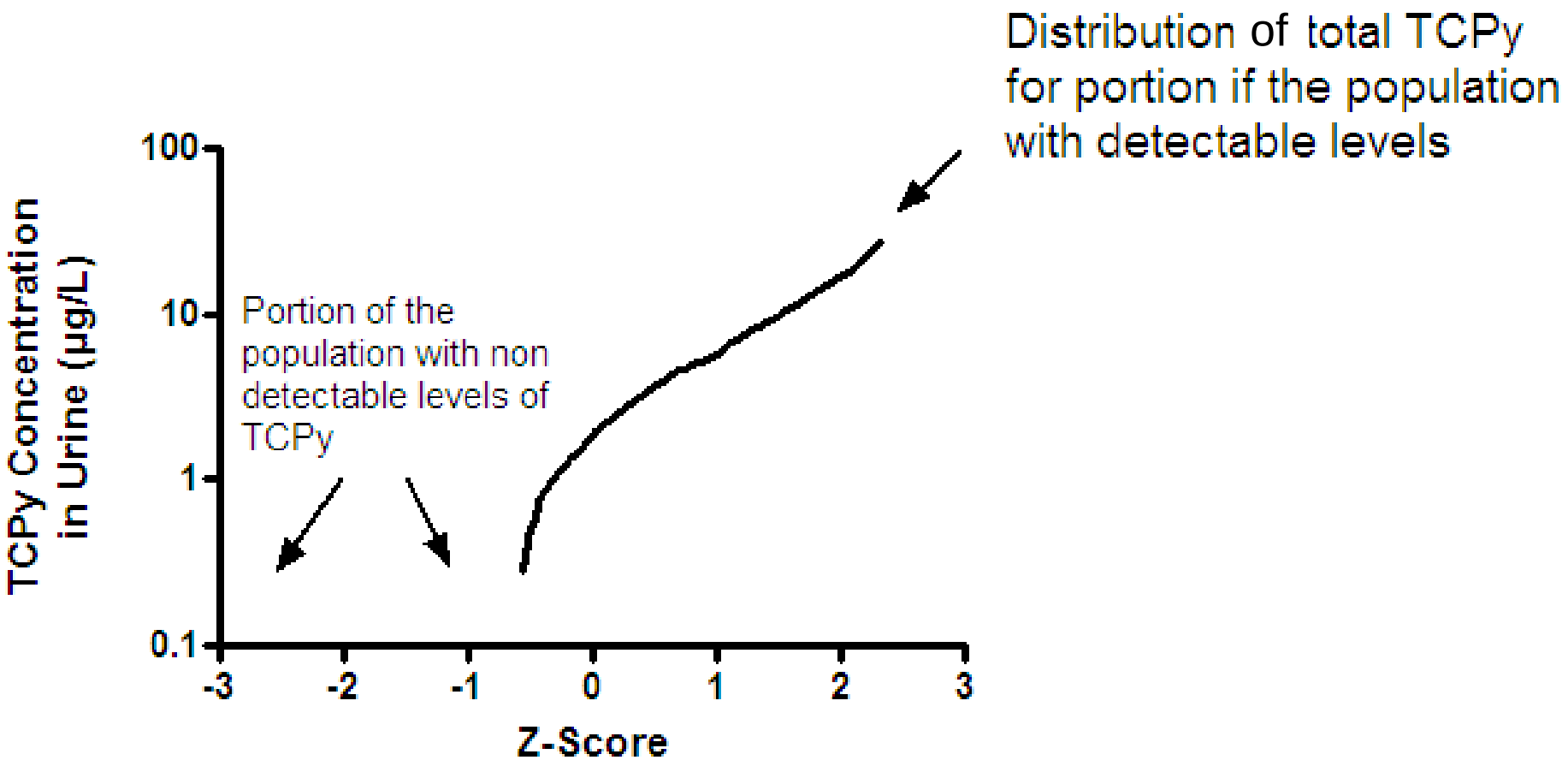


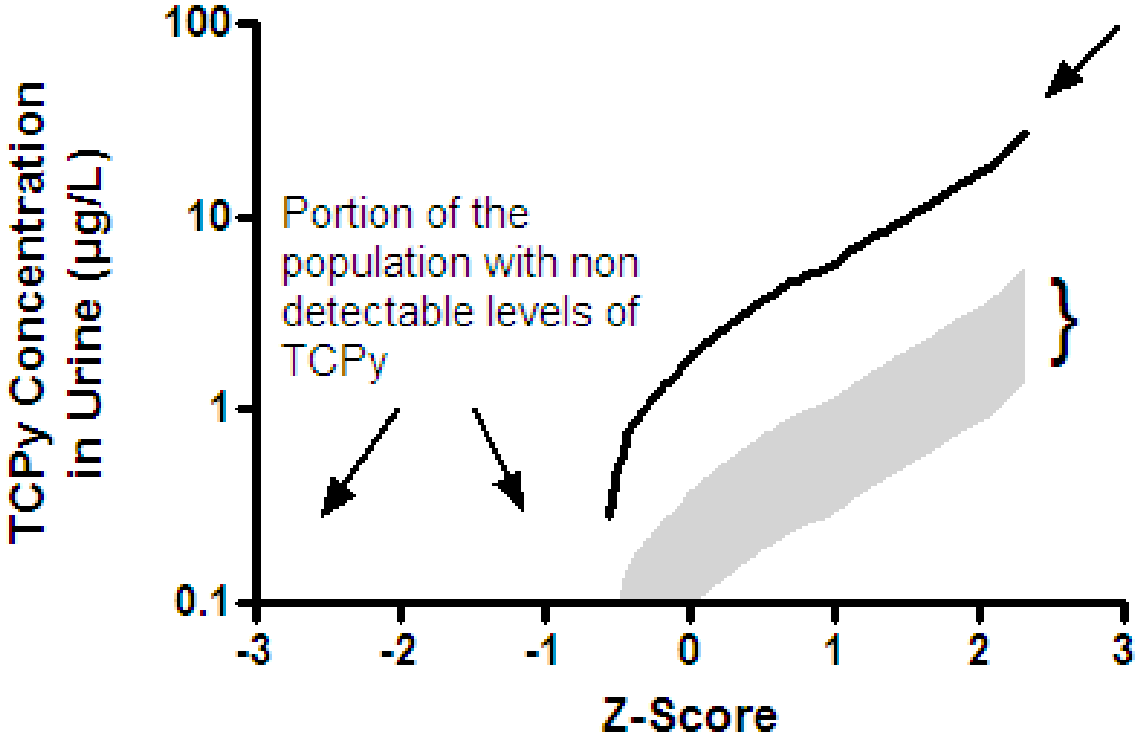
Comparison to TCPy data

- NHANES data:
  - Data collected in 2002 limited to 12yr and older
  - Spot urine sample
- NHANES data on TCPy reflects:
  - Dietary intakes of TCPy, CPF, and methyl-CPF
  - TCPy produced by metabolism of CPF residues in diet is believed to be between 5 and 20% of total TCPy

Comparison to NHANES data



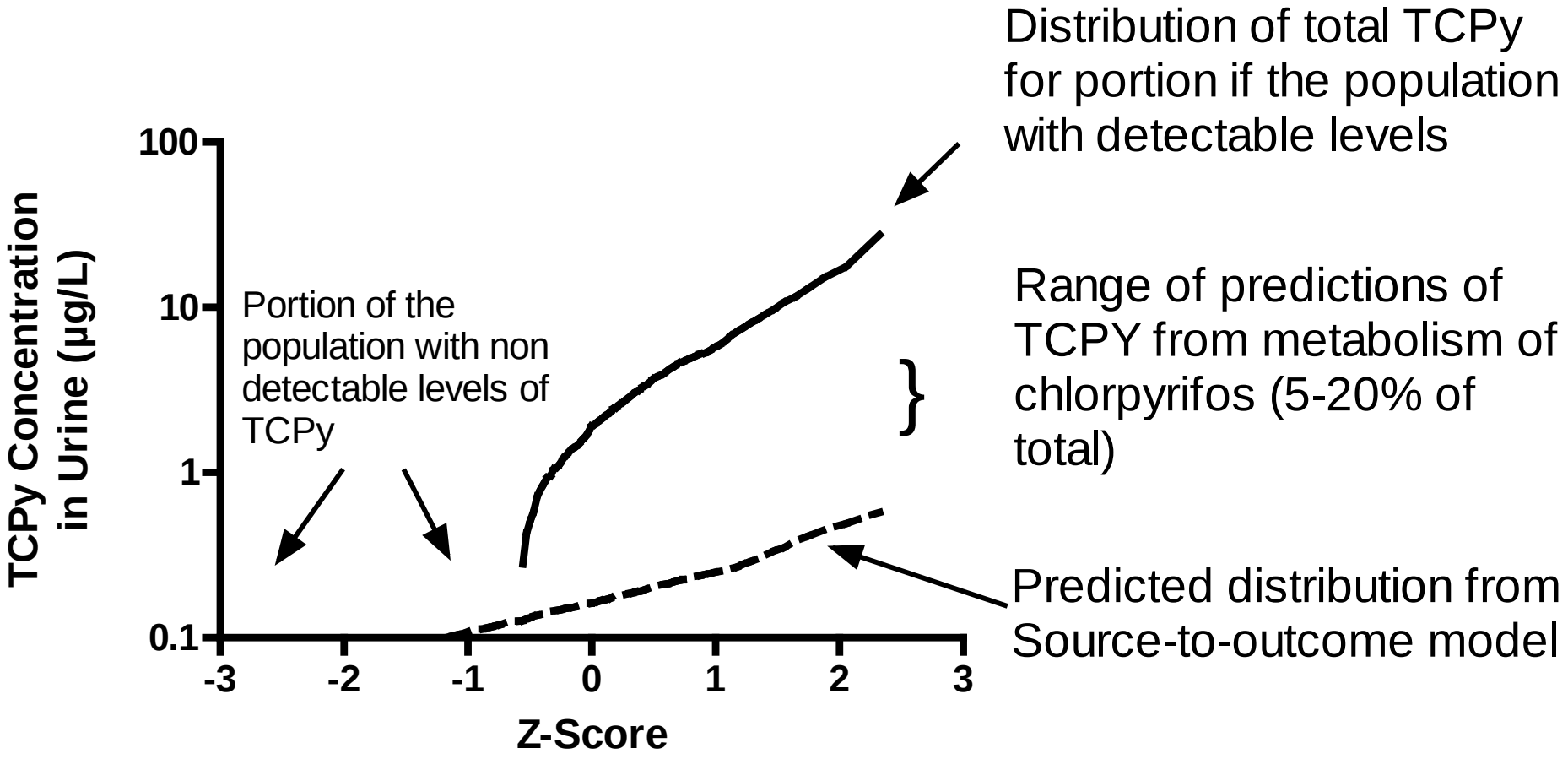
Comparison to NHANES data



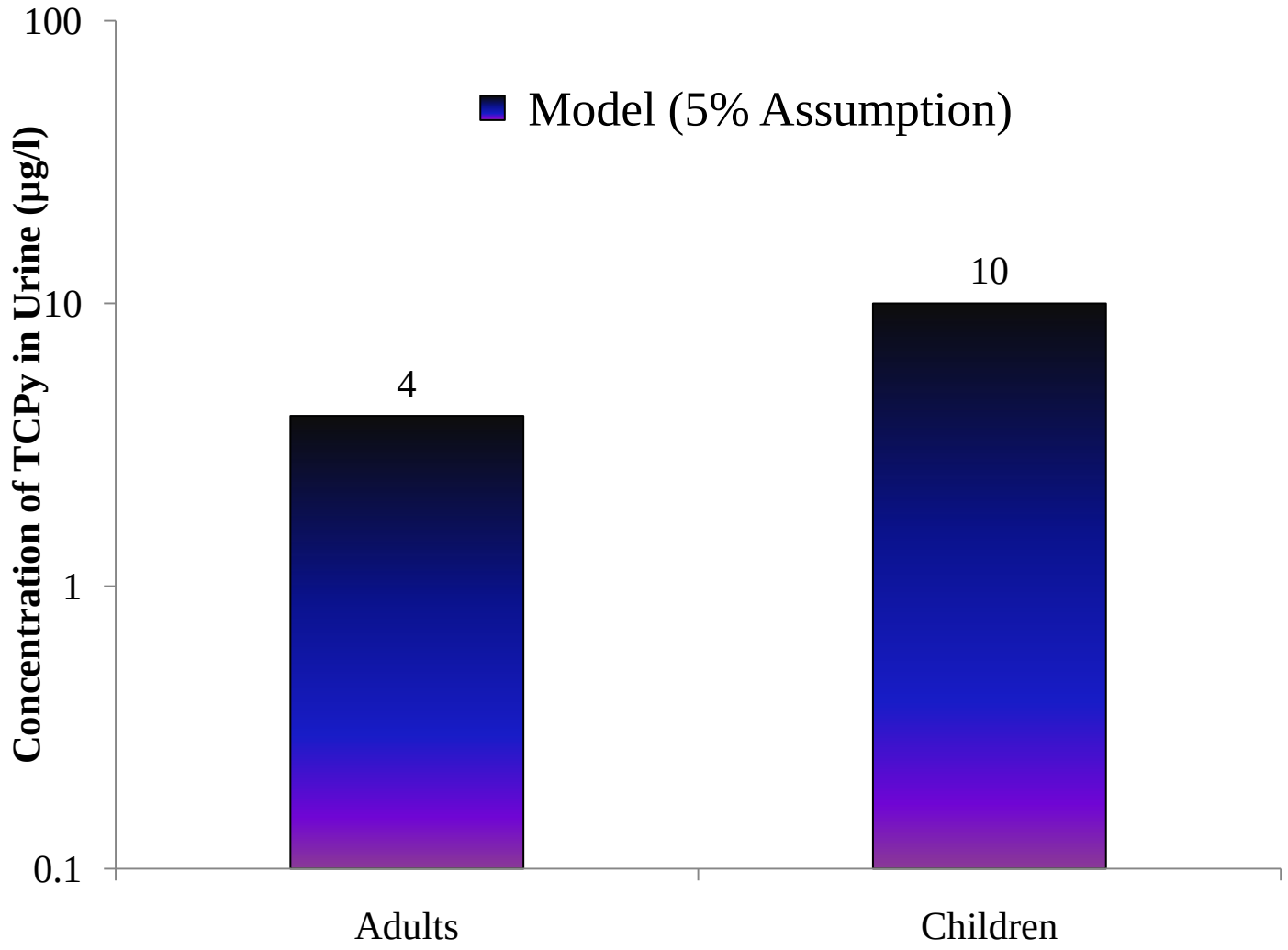
Distributior of total TCPy for portion if the population with detectable levels

Range of predictions of TCPY from metabolism of chlorpyrifos (5-20% of total)

Comparison to NHANES data



Comparison of observed levels of TCPy in urine and model predictions



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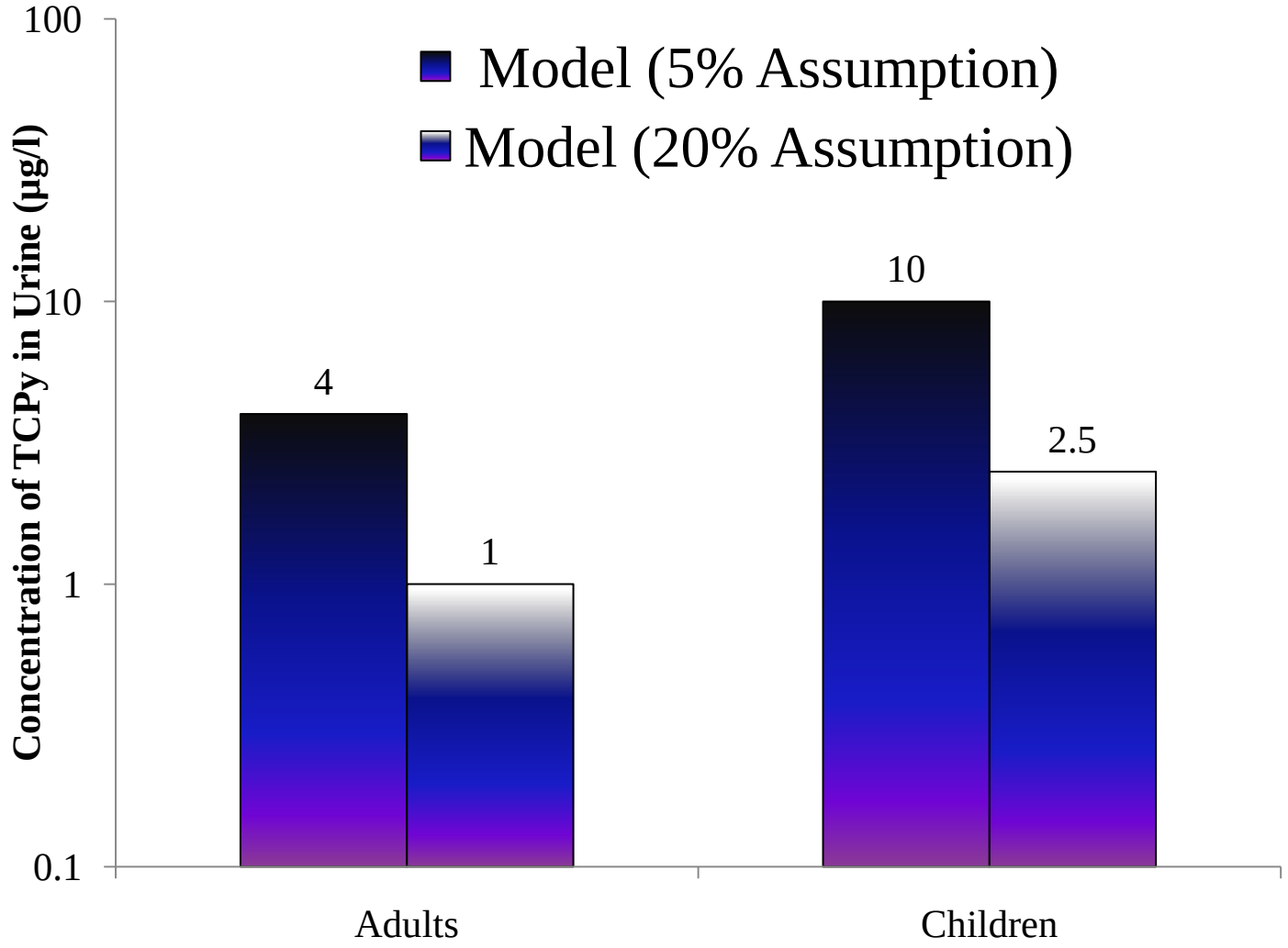
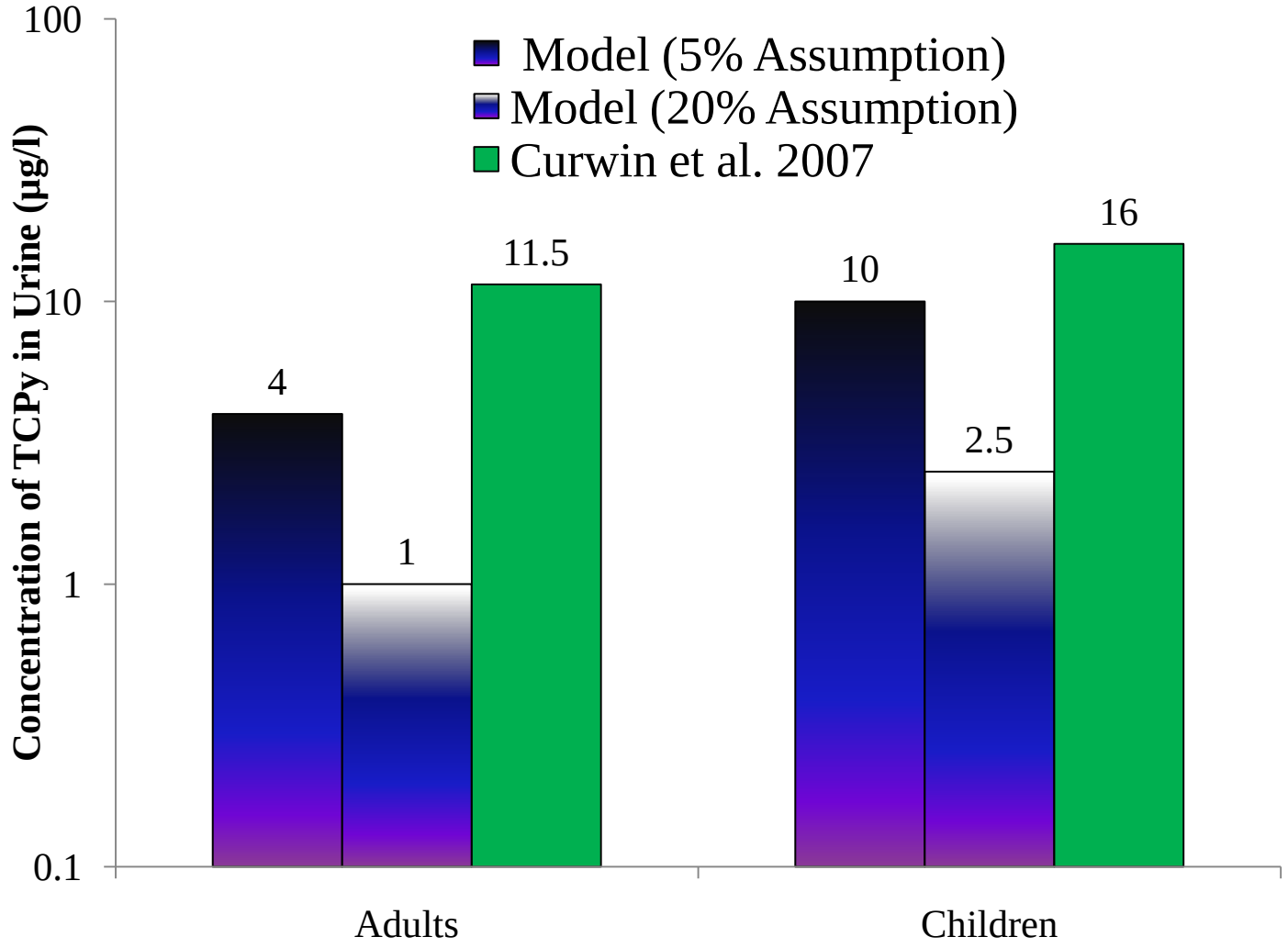


Comparison of observed levels of TCPy in urine and model predictions



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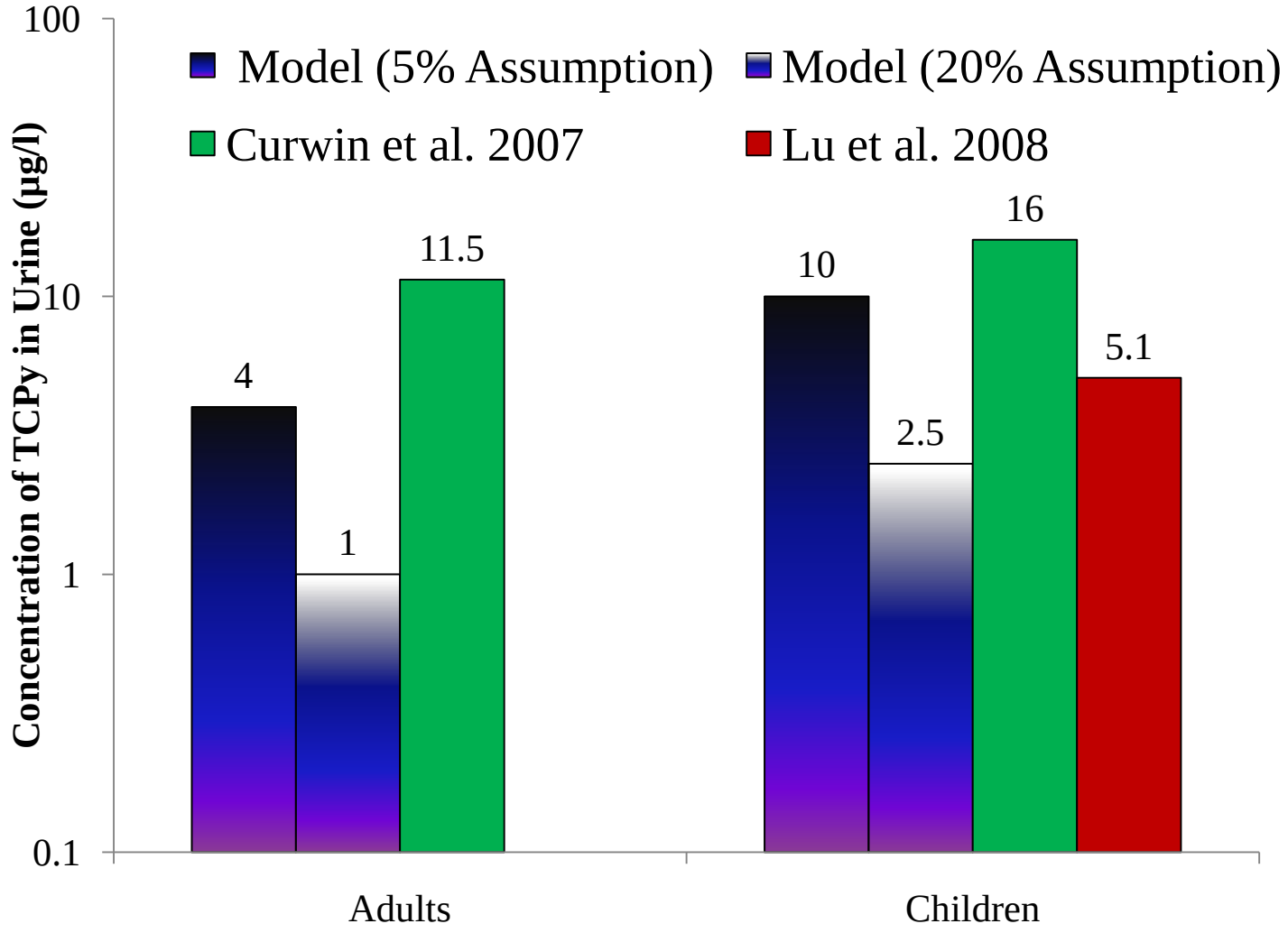

Conclusions

- The portions of source-to-outcome model have been evaluated by comparison to human volunteer studies
  - Measure of central tendency for groups of individuals (LifeStage model)
  - Measure variation across individuals (Variation model)
  - Variation model over predicts response
- The predictions of the exposure and PBPK portions of the model matched the monitoring data